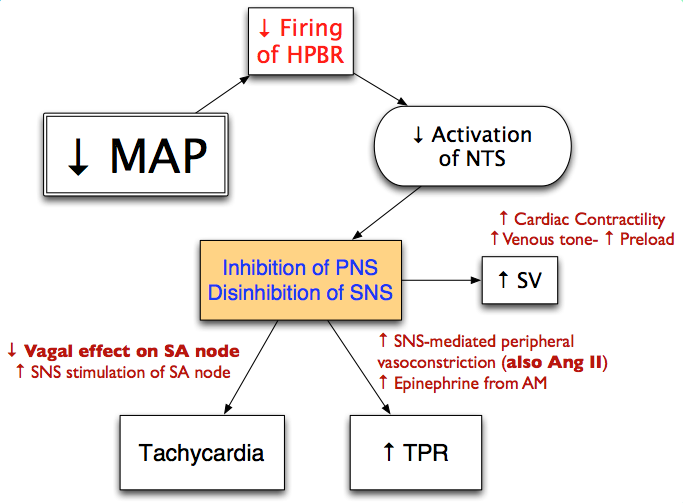
**Sensors, Regulators and Effectors**

* CO = P/TPR
* P= CO \* TPR
* P= HR \* SV \* TPR
* P = HR \* (EDV-ESV) \* TPR
* \*\*HR is the most modulated factor in acute regulation of MAP
  + the next modulated factor is TPR
* Short term regulation of MAP primarily involved the SNS and the regulation of HR and TPR

**High Pressure Baroreceptors (HPBR)**

* These HPBR sense a CHANGE IN PRESSURE
  + They are actually responding to a CHANGE IN STRETCH🡪 stretch activated Ca channels (ex: TRPC1) that are activated/inactivated when aortic wall is deformed
  + So if you have ↑ MAP but no stretch change (like in dz’s that ↓ aortic compliance 🡪 aortic fibrosis /atherosclerosis) then these HPBR don't respond
* They are located in aortic arch and carotid sinus
* If there is a ↑ MAP 🡪 ↑ in stretch of aortic wall (termed LOADED) 🡪 activation of HPBR 🡪 opening of stretch activated calcium channels 🡪 membrane depolarizes 🡪 sends depolarization signal along nerves of the PSNS—CN IX (glossopharyngeal) and CN X (vagas) 🡪 NTS (nucleus tractus solitarii) in the Medulla 🡪 activation of PSNS preganglionic neurons (DMN-dorsal motor nucleus of the vagus & NA-nucleus ambiguous)🡪 ↓ HR🡪 ↓ CO 🡪 ↓ MAP
  + NTS also sends an inhibitory signal to Sympathetic preganglionic neuron (vasomotor area) 🡪 vasoconstrictor tone is lost 🡪 ↓ TPR 🡪 ↓ in MAP
* If there is a ↓ in MAP🡪 ↓ in stretch of aortic wall (termed UNLOADED) 🡪 ↓ stretch activated calcium channels 🡪 ↓ in firing of HPBR 🡪 not activate NTS 🡪 will not have stimulation of PSNS and will have continued stimulation of SNS 🡪 vasoconstriction 🡪 ↑ TPR --↑ MAP
* PSNS regulates…
  + ↓ HCN (funny current channels responsible for automatic phase 4 depol)🡪 ↓ phase 4 depol of SA node
  + ↓ slope of phase 0
  + ↑ in conduction delay—AV node less responsive (not blocked just slowed🡪 longer PR interval)
* SNS regulates
  + ↑ HR via the SA node and ↑ cardiac contractility (b/c ↑ intracellular calcium)
  + modulation of TPR via change in diameter of arterioles (causes vasoconstriction🡪 ↑ in TPR)
  + Stimulation of adrenal medulla to release Epinephrine
  + Activates RAS in kidney
* Effects of SNS activation on VSM @...
  + α1 receptors on VSM
    - Gq🡪 PLC🡪 ↑ IP3/DAG🡪 ↑ Ca and Calmodulin Kinase phosphorylates MLCK🡪 P MLC 🡪 contraction 🡪 ↑ TPR🡪 ↑ MAP
    - blocking α1- receptors 🡪 ↓ in BP
  + β2 Receptors
    - Gs
    - Will vasorelax through the inhibition of MLCK
* After cardiac transplant the heart’s response to ↑ MAP will be none b/c the heart is denervated but vascular response (changing TPR) will still be there.
* Example Exam Q: 2 y/o pt went into OR for removal of his tonsils. He had bleeding during the surgery so surgeon put NE on wound. The NE is rapid absorbed and caused ↑ in MAP so surgeon gave α1 blockers. What is the response of HPBR?
  + If you block α1 receptors you get no SNS stimulation so you see vasodilation 🡪 ↓ in TPR 🡪 ↓ MAP 🡪 HPBR inactivated 🡪 ↑ in SNS & ↓ in PSNS 🡪 ↑ HR and vasodilation due to β2 Receptors (remember α1-receptors are blocked)
* Under “normal” homeostatic conditions vagus input to SA node keeps a low HR and tonic sympathetic outflow from C1 area (vasomotor area) maintains resting vascular tone
* Tachycardia observed when NTA is inhibited is more dependent on inhibition of vagus to the heart rather than direct SNS-mediated stimulation of HR
* Continuous vasoconstrictor tone from the vasomotor center (SNS) maintains arterial pressure
  + Sprinal block via injection of anesthetic –blocks SNS tone from medulla🡪 arterial pressure ↓~50% .
    - NE can still elicit a constriction (vessels are responsive)
* 
  + ↑ in cardiac contractility🡪 ↑ in preload
  + ↑ Venous tone 🡪 ↑ venoconstriction 🡪 ↑ BF to heart from veins 🡪 ↑ preload🡪 ↑ cardiac performance 🡪 ↑ SV

**Secondary Contributors of the Acute Regulation of MAP**

* Peripheral Chemoreceptors (more important for inspiration)
  + Located in the aortic body and carotid body
  + Low PO2 activates the afferent signal that stimulates the NTS (PSNS) AND the vasomotor area (SNS)🡪bradycardia and vasoconstriction
    - ↓ PO2 then ↓ O2 in blood so that O2 needs to be on heart and brain cuz those matter more
* Central Chemoreceptors
  + Medullary receots that primarily detect ↑ PCO2
  + Activates vasomotor area to produce vasoconstriction (SNS)
* Thus hypoventilation or diffusional problems ↓ PO2 and ↑ PCO2 causing reflex vasoconstriction and bradycardia

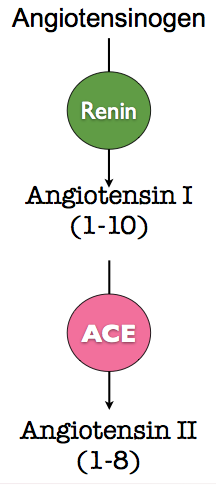
**Standing Up/Erect Posture**

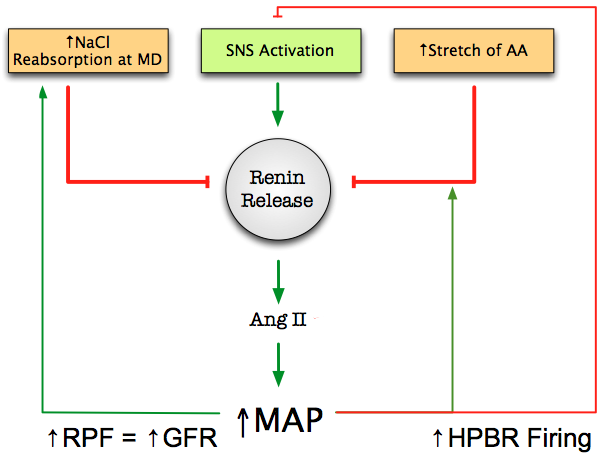
* Veins have large compliance () so when you stand up gravity comes into play🡪↑ absolute pressure to large veins🡪 ↑ volume of the blood in veins🡪 veins change their shape and become circular and they store/pool blood🡪 🡪↓ blood to heart 🡪 ↓ preload/EDV 🡪 ↓ cardiac performance 🡪 ↓ SV 🡪 ↓ CO=↓ BP 🡪 ↓ MAP 🡪 ↓ HPBR (unloading) 🡪 inhibit NTS and vasomotor area is active 🡪 Tachycardia, Arteriolar Constriction , Veno-constriction
  + THIS HAPPENS EVERYTIME YOU STAND UP
  + If a pt is on α1 blocker arteriolar constriction and venoconstriction can’t occur so BP will ↓ when they stand up = ORTHOSTATIC HYPOTENSION

**Measuring Sensitivity of HPBR**

* To measure use neck pressure by putting suction cups on neck near carotid sinus
  + Negative pressure 🡪 deforms carotids and mimicks ↑ in MAP b/c of stretching 🡪🡪 bradycardia and vasodilation 🡪 ↓ MAP
    - Will see bradycardia by larger distance between QRS waves on EKG
  + Positive pressure 🡪 ↓ stretching mimicks ↓ in MAP 🡪🡪 tachycardia and vasoconstriction 🡪 ↑ in MAP

**Extracellular Fluid Volume**

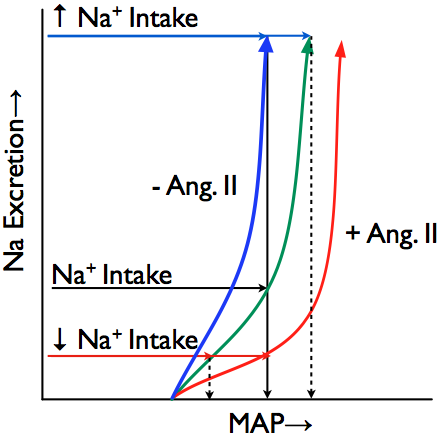
* ECF is the true LONG TERM regulator of arterial pressure b/c HPBR are adaptable –they stop responding to chronic changes in MAP by making the change their new baseline
* ↑ in ECF Volume (ECFV) 🡪 ↑ BV 🡪 ↑ VR🡪 ↑ Preload 🡪 ↑ SV 🡪 ↑ CO = ↑ BP 🡪 ↑ MAP
* ↓ in ECF Volume (ECFV) 🡪 ↓ BV 🡪 ↓ VR🡪 ↓ Preload 🡪 ↓ SV 🡪 ↓ CO = ↓ BP 🡪 ↓ MAP
* BUT! b/c MAP is more important to keep constant, changes in MAP actually dictates the ECFV
  + So ECFV is used to keep MAP constant in chronic regulation
  + If ECFV strickly determined MAP then when you eat a sodium packed meal if ECFV dictated MAP then you would constantly be having ↑ and ↓ in MAP
    - Na is linked to ECFV due to osmolality (conc. Of solutes in a solvent)—So water always follows sodium
    - Osmolality is always equal in every compartment
  + So ↑ in MAP you want to get rid of ECFV to get MAP back to normal—just get rid of Na to ↓ ECFV
* Arterial pressure (MAP) has a direct negative feedback on renal function (renal function regulates ECFV) thus indirectly regulating ECFV
  + 2 mechanisms
    - Renin Angiotensin System
    - Pressure Natriuresis mechanism
* Kidney
  + Macula Densa
    - It is a juxtaglomerular apparatus (JGA) where the afferent arteriole of the glomerulus touches the Thick ascending limb
* Renin Angiotensin System (RAS)
  + 
  + Angiotensinogen is secreted by the liver
    - Abundantly available
  + Renin is secreted by the kidney’s macula densa
    - RAS is regulated by Renin🡪 THIS IS RATE LIMITING
  + AT I is biologically inactive and is 1-10 aa long
  + ACE- Angiotensin converting enzyme is on all endothelium but mostly in the lungs converts AT I 🡪 AT II which is biologically active and this going into circulation
  + Renin/AT II causes Na and Water RETENTION 🡪 ↑ in ECVF 🡪 ↑ in MAP



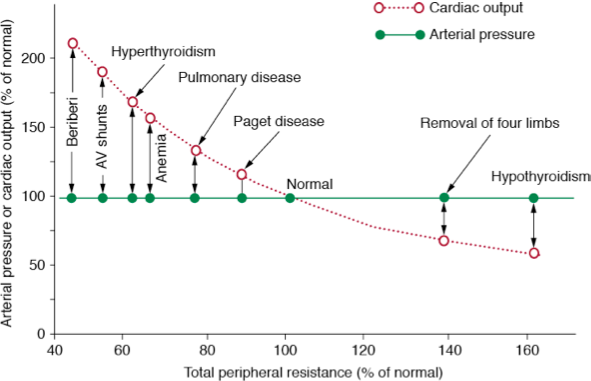
* SNS activation activates β1 Receptors on macula densa causing Renin release
* AA= afferent arteriole in the MD
  + ↑ MAP 🡪 ↑ stretch of AA 🡪 ↓ renin 🡪 ↓ AT II 🡪 ↓ MAP
  + ↑ MAP 🡪 ↑ RPF (renal plasma flow) 🡪 ↑ GFR (glomerular filtration rate) 🡪 ↑ NaCl reabsorbtion at MD 🡪 ↓ in Renin/ AT II 🡪 ↓ in MAP
  + ↑ in MAP 🡪 ↑ HPBR firing 🡪 suppression of SNS 🡪↓ β1 activation on MD 🡪 ↓ renin 🡪 ↓ AT II 🡪 ↓ MAP
* AT II (AT1)
  + Acute effects
    - ↑ TPR 🡪 ↑ MAP
    - AT1 receptor🡪 vasoconstriction 🡪 ↑ TPR 🡪 ↑ MAP
      * Stronger than NE
    - ↑ SNS activity (similar effects to **cocaine**)
      * ↑ NE release
      * ↓ NE reuptake
      * ↑ peripheral responsiveness
      * ↑ CNS discharge
    - Secretion of Epinephrine from adrenal medulla
  + Chronic effects
    - Alters Renal Function
    - ↑ Na-H exchanger in proximal tubule of kidney🡪 Na retention
    - Aldosterone release 🡪 Na retention
    - Altered renal hemodynamics🡪 solute reabsorption
    - ↑ in Na retention/reabsorption in the kidneys🡪 ↑ ECFV b/c water follows Na 🡪 ↑ MAP 🡪 ↓ renin 🡪 ↓ AT II 🡪 salt and water excretion 🡪 ↓ ECFV 🡪 ↓ MAP

**Pressure Natriuresis Curve**

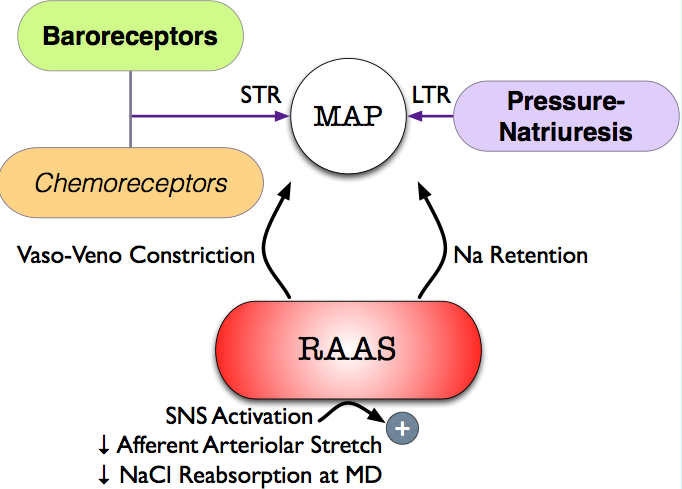
* ↑ MAP 🡪 ↑ pressure in the capillaries along the tubule of the nephron 🡪 ↑ RPF🡪 ↑ GFR 🡪
* The primary mechanism by which the kidneys regulate BV is by adjusting the excretion of H20 and Na into the urine.
  + ↑ BV🡪 ↑ MAP🡪 ↑ RPF 🡪 ↑ GFR 🡪 which causes ↓ reabsorption🡪 ↑ [Na] and [Cl] in the filtrate. The MD senses this ↑ and trigger an autoregulatory response to further ↓ reabsorption of ions and water🡪 ↑ EXCRETION of Na 🡪 ↓ ECFV 🡪 ↓ MAP
* ↑ in hydrostatic pressure in the peritubular capillaries ↓ solute and water reabsorption 🡪 ↑ Na excretion 🡪 ↓ ECFV 🡪 ↓ MAP



* P-N curve only predict that if you have ↑ MAP then you Na excretion will ↑
  + RAS makes sure Na intake = Na output
  + No AT II (↓ MAP) causes the curve to shift to the L
  + Addition of AT II (↑ MAP) causes the curve to shift to the R



* A sudden ↑ in TPR wont sustain HTN for long
  + ↑ in TPR CANT be the cause of HBP b/c PN kicks in 🡪 ↓ in ECFV 🡪 ↓ CO 🡪 balances eqn
    - also RAS is suppressed🡪 ↑ Na excretion 🡪 ↓ in ECFV 🡪 ↓ CO 🡪 balances eqn
  + CO = MAP \* TPR so if you ↑ TPR and you want MAP to be the same then change CO
  + BUT! If you have a chronic problem with your kidneys the PN curve doesn't apply
    - So if you have selective vasoconstriction of the renal bed over a long period of time you will get ↑ MAP
      * THIS IS THE CAUSE OF 90% of essential HTN = HBP in the absence of a clinically identifiable secondary pathology (↑ TPR is usually a consequence of this)
  + ↑ TPR (think ↑ vasoconstriction )—SNS causes vasoconstriction so if you have overactive SNS then you can have ↑ TPR (seen in pheochromacytoma)
    - SNS activates RAS so ↑ SNS activity causes ↑ in AT II (which is a vasoconstrictor) 🡪 ↑ TPR 🡪 ↑ MAP
    - AT II also ↑ Na retention so double whammy you get ↑ in TPR and ↑ in ECFV 🡪 ↑ ↑ MAP
    - One of the leading causes of HTN! Which is why AT II blockers are so successful in tx’ing HTN
  + ↑ TPR is usually a consequence rather than a cause of essential HT
    - Rightward shift of PN curve 🡪 ↑ MAP at normal salt 🡪 Tissue vasoconstriction—autoregulation 🡪 ↑ TPR 🡪 ↑ MAP



* STR= short term regulation
* LTR= long term regulation